January 20, 2000
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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Ladies and Gentlemen:

Subject: Suitability Determination for Donors of Human Cellular and Tissue Based Products, Docket No. 97N-484S

The Orthopedic Surgical Manufacturers Association (OSMA) welcomes the opportunity to provide comments on FDA's proposed rule to require tissue banks and manufacturers of human cellular and tissue-based products to screen and test donors for risk factors for and clinical evidence of relevant communicable disease agents and diseases, which FDA published in the *Federal Register* on September 30, 1999.

I. Background

OSMA was formed over 45 years ago and has worked cooperatively with FDA, the American Academy of Orthopedic Surgeons (AAOS), the American Society for Testing and Materials (ASTM), and other professional medical societies and standards-development bodies, to ensure that orthopedic medical products are safe, of uniform high quality, and supplied in quantities sufficient to meet national needs. Association membership currently includes member companies producing over 90 percent of all orthopedic implants intended for clinical use in the United States, and provides significant jobs and income for these U.S.-based companies through their global distribution systems.

OSMA strongly supports the principle of donor screening to prevent the transmission of communicable disease from infected donors, and believes that the measures outlined in FDA's proposed donor suitability rule are basically sound. We have strong reservations, however, about certain aspects of FDA's proposal. OSMA's comments on specific provisions of the proposed rule are provided in Exhibit I. At the same time, of greatest concern, are FDA's attempts to regulate tissue in a burdensome and non-transparent manner which is described below.

OSMA continues to have significant questions and reservations about the "minimal manipulation" and "homologous use" criteria FDA is using to determine whether particular tissue-based products will be treated as conventional tissues or as medical devices or biological products subject to regulation under the Federal Food, Drug, and Cosmetic Act. Because the preamble accompanying the proposed donor suitability rule provides further discussion of the criteria FDA says it will use to make jurisdictional

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determinations for tissue-based products, OSMA is setting forth its views on the criteria in these comments.

In addition, because OSMA believes the criteria FDA will use to make jurisdictional determinations cannot be judged separately from the process by which the agency will apply the criteria, OSMA is also submitting comments on the lack of procedures and openness by which the agency's Tissue Reference Group is using to make jurisdictional determinations.

II. FDA's Criteria and Procedure for Jurisdictional Determinations

1. "Minimal Manipulation" and "Homologous Use"

OSMA believes that FDA's definitions of "minimal manipulation" and "homologous use" offers imperfect and uncertain guidance for determining what tissues should be regulated as devices, drugs, biologics, or tissues. OSMA believes that rigid application of these definitions will lead to the imposition of inappropriate and burdensome labeling, processing, data submission, and other requirements for conventional tissues that are currently used by clinicians and have been in use for many years.

As FDA applies its proposed criteria in practice, OSMA expects that there will be occasions when the agency and the medical community disagree over whether a specific product has been only "minimally manipulated" or is being put by physicians to a "homologous use." Also, while there may be cases where there is agreement on the application of the criteria, there will be disagreement about the appropriateness of the regulatory requirements imposed. OSMA believes that such disagreements should be identified and resolved through transparent, open and early communication between FDA and the medical community.

There are clear public health benefits in maintaining a safe and continued supply of tissue to the medical community and the patients who require them. OSMA believes that the current regulations dealing with donor suitability with the qualifications stipulated in Exhibit I are sufficient to support the safe and effective use of human allograft tissue. Unnecessary and overly burdensome regulations, in the absence of Good Tissue Practice (GTP) regulations, are premature, inappropriate and at variance with FDA's stated objectives (and Congressionally mandated) of "least burdensome" practice of regulation. Such a regulatory practice is considered arbitrary, at best, and would likely disrupt the availability of quality materials. In fact, such action may promote the proliferation of hospital or other intrastate based suppliers, thereby frustrating the very interests of FDA and OSMA in maintaining safe and available supplies.

2. The Tissue Reference Group (TRG)

In early June 1999, OSMA received notification from Dr. Celia Witten of CDRH, advising that the Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee would be meeting on July 27, 1999, to "focus on the classification of bone dowel devices of human origin" and inviting OSMA and its members to participate in the panel meeting by presenting testimony and/or submitting written comments. From this language, OSMA concluded that CDRH had already determined that bone dowels should be regulated as medical devices under the FD&C Act. This was later confirmed

in direct discussions with CDRH. OSMA presented its position to FDA at that time, where OSMA strongly disagreed with FDA's position. OSMA continues to object to FDA regulation of bone dowels as medical devices, among other objections.

We now understand that the preliminary determination to treat bone dowels as medical devices was based on a TRG meeting in the fall of 1998. Though FDA subsequently revised the agenda of the classification panel meeting to eliminate consideration of the bone dowel issue, the procedure used by the agency to determine that bone dowels should be treated as medical devices remains of great concern to OSMA and its members.

The TRG apparently holds the view that it has authority to respond to requests for designation from individual product sponsors by issuing either a determination for a particular product or a "recommendation" for an entire class of products. According to the TRG's Annual Report for fiscal year 1998, the TRG has authority to make recommendations for a specific product or for a class of products. Even when the TRG takes action that purports to apply only to a specific manufacturer's product, the action is likely to serve as a precedent for all products in the same class and thus amounts to class-wide regulation. Indeed, there is an argument that failing to apply a product-specific regulation to other similarly situated products would be subject to challenge as arbitrary and capricious. In issuing class-wide recommendations, the TRG purports to "communicate this information through guidance and revisions of regulations where appropriate." Nothing in current FDA regulations or in the TRG's Standard Operating Procedures requires the TRG to allow interested parties the opportunity to participate in its proceedings, which might result in a "recommendation" for regulation affecting an entire class of tissue-based products.

FDA regulations do not permit the Office of the Ombudsman to issue class-wide jurisdictional determinations based on a request for designation from a single manufacturer. Under 21 C.F.R. Part 3, a sponsor of a premarket approval application or investigational filing for a product is permitted to submit a Request For Designation (RFD) to the Office of the Ombudsman where the "agency component with primary jurisdiction [of the product] is unclear or in dispute." Within 60 days of the filing dare, the Ombudsman is required to "issue a letter of designation to the sponsor... specifying the agency component designated to have primary jurisdiction for the premarket review and regulation of the product at issue and any consulting agency components." (emphasis added). This regulation does not authorize the Ombudsman to respond to the RFD with a letter of designation covering all products in the class.

FDA should clarify the TRG's authority. At minimum, OSMA believes the agency should amend the Standard Operating Procedures followed by the TRG to preclude the Group from issuing class-wide "recommendations" based on an assessment of a single product. OSMA also urges FDA to: (1) issue a public announcement whenever the TRG determines that a specific tissue-based product is to be regulated under the FD&C Act; and (2) provide general notice whenever the TRG concludes that an RFD might become the basis for treating an entire class of tissue-based products as medical devices or biological drugs under the FD&C Act.

With respect to TRG proceedings, generally, FDA should institute the following general procedures for any action taken or proposed by the TRG, which could have broad effects on the tissue industry.

First, TRG meetings should be announced by publication in the *Federal Register* or in some other formal fashion, together with a general description of the issues to be discussed. To OSMA's knowledge, nothing in the TRG's standard operating procedures assures that all interested parties, including companies directly affected by a decision, will be given notice that the TRG intends to consider the jurisdictional status of a particular product.

Second, TRG meetings should be open to the public, subject to the confidentiality requirements in federal law and FDA regulations. The TRG has taken the position that its meetings are not required to be open because proprietary information is submitted by the sponsor requesting the ruling. In fact, FDA routinely holds open meetings on subjects involving proprietary information, closing only those portions of the meeting that require the disclosure of confidential data.

Third, the TRG's standard operating procedures should direct the Executive Secretary of the Group to publicize the group's findings and the basis for its decisions, subject to the confidentiality requirements in federal law and FDA regulations, and that the TRG's standard operating procedures should require the Group to explain jurisdictional determinations of the basis of published criteria.

OSMA acknowledges that the TRG has been operating for more than two years and has made recommendations for more than ten cellular and tissue-based products. OSMA further recognizes that FDA has limitations on its resources to implement the tissue program. In our view, however, the current TRG procedures must be improved to address the legitimate concerns of the medical community to ensure a fair and equitable consideration. FDA must recognize that significant financial investments have been made in these technologies, and unnecessary FDA action could put these investments at risk.

We trust you find these comments of value, and we request the opportunity to discuss these concerns with the FDA directly should the FDA not agree with our comments.

We thank you for the opportunity to comment.

Sincerely,

ORTHOPEDIC SURGICAL
MANUFACTURERS ASSOCIATION

Thomas L. Craig, President

EXHIBIT I

Comments on Specific Provisions

1. Definition of "Human Cellular or Tissue-Based Product" (Proposed Section 1271.3(h)

The proposed definition of "human cellular or tissue-based product" in proposed Section 1271.3(e) includes not only products containing human cells or tissues, but also any "cell or tissue-based" component of such a product. OSMA does not believe that this definition would cover a component, such as an extract, that is incorporated into a product that contains no other tissue component, because the extract itself is not a human cell or tissue. FDA should clarify the scope of this part of the proposed definition.

2. Definition of "Donor Medical History Interview" (Proposed Section 1271.3(o)

The proposed definition of "donor medical history interview" does not specifically state that interviews with sources of information about a prospective donor must be in person. Interviews should not be limited to an in-person, face-to-face dialogue, and that the proposed definition should be amended specifically to include written exchanges, telephonic communications, and other forms of communication. OSMA assumes that the definition includes communications with friends and life partners who are often valuable sources of information about prospective donors.

3. Procedure for Identifying Additional "Relevant Communicable Disease Agents or Disease Means" (Proposed Section 1271-3(y)

FDA should specify, in the final rule itself, the procedures it will use to identify additional "relevant communicable disease agents and diseases." FDA would be required by law to give prior notice and afford interested parties an opportunity to comment before adding a new agent or disease to the list under Section 1271.3(y), except where there is an imminent and overriding public health need.

The medical community might be able to provide FDA with information relevant to the determination whether a new disease or disease agent should be added to the list. In some cases, comments on a proposed plan to require testing for a new disease or disease agent could reveal scientific complexities otherwise unknown to FDA. In addition, with these procedural safeguards, FDA could avoid imposing an additional testing obligation where there is no test available for a new disease. Through comments, the medical community also could help FDA avert the unnecessary destruction of tissues already in inventory based on a precipitous decision to add a new disease or disease agent to the list if inventoried tissues are for some scientific reason not amenable to testing.

4. Requirement That "Suitability" Determination Be Based on Both Screening and Testing(Proposed Section 1271.50)

OSMA supports proposed Section 1271.50 which provides that a donor is deemed "suitable" based on acceptable results of both screening and testing, because this will assure that a prospective donor deemed unsuitable based on an initial screening and covered by proposed Section 1271.65 will be subject to mandatory testing.

5. Requirement That Donor Specimen Be Collection At the Time of Recovery or Within 48 Hours(Proposed Section 1271.80(b)

OSMA is concerned that proposed Section 1271.80(b) imposes unduly restrictive time requirements on tissue recovery operations. For cadaveric donors (who are the overwhelming majority of donors), the proposed regulation would require tissue banks to collect blood specimens for testing "at the time of recovery... or within 48 hours after recovery." Though it is often desirable to obtain a blood sample for testing as close to the time of death as possible, there can be valid scientific reasons for drawing a specimen pre-mortem. The red blood cell content of post-mortem samples is often affected by hemolysis and hemodilution, both of which

can be aggravated by some types of medical intervention. Hemolysis and hemodilution can lead to false positives and the unnecessary disqualification of tissue from cadaveric donors.

In OSMA's view, amending the proposed regulation to permit pre-mortem testing for cadaveric donors is scientifically justified. Such donors generally are hospitalized, and thus their exposure to communicable disease agents and diseases is limited immediately before death. Consistent with this view, FDA is proposing to permit testing up to seven days prior to recovery for living donors, whose exposure to disease immediately before donation will generally be greater because they are not hospitalized.

6. Requirement That Testing Be Performed Using Only FDA Licensed, Cleared, or Approved Products in Accordance with Approved labeling by CLIA-Certified laboratories (Propose Section 1271.80)

Proposed Section 1271.80(c) should be amended to describe the circumstances in which tissue establishments are permitted to use tests that are not FDA-licensed, -cleared, or -approved. As FDA has recognized, there are diseases and disease agents for which an FDA-licensed, -approved, or –cleared test does not exist. There are also diseases and disease agents for which there is a test that has been licensed, approved or cleared by FDA, but for use only in blood, rather than tissue. In those cases, manufacturers should be permitted to use other appropriate screening measures.

This section should be amended to permit testing by laboratories that are not certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) but are exempt from CLIA because they are in States (e.g. New York) whose clinical laboratory requirements have been found by the Department of Health and Human Services to be equivalent to or more stringent than CLIA requirements. This section should further be amended to permit testing by foreign laboratories that are subject to requirements that are equivalent to or more stringent than analogous requirements under CLIA.

7. Scope of Regulation of Tissue Screening and Testing Laboratories

FDA should clarify that clinical laboratories are not "establishments" subject to registration and listing with FDA simply because they perform communicable disease testing under contract with tissue banks. FDA states in the preamble to the proposed donor suitability rule that "communicable disease testing and screening [are]...steps in the manufacturing process" and notes that the proposed registration and listing rule defines "manufacture" to include "screening" and "testing."

Facilities whose only role in tissue processing is testing are already excluded from the proposed registration and listing requirements because the proposed definition of "establishment" expressly excludes "an individual...under contract to a registered establishment." In addition, because the proposed donor suitability rule provides that all testing must be performed in laboratories that are certified under the Clinical laboratory Improvement Amendments of 1988 (CLIA), requiring registration for these laboratories is unnecessary. In contrast, facilities engaged in "screening" of prospective tissue donors should be deemed "establishments" under the proposed establishment registration and listing rule because these facilities are not necessarily governed by CLIA.

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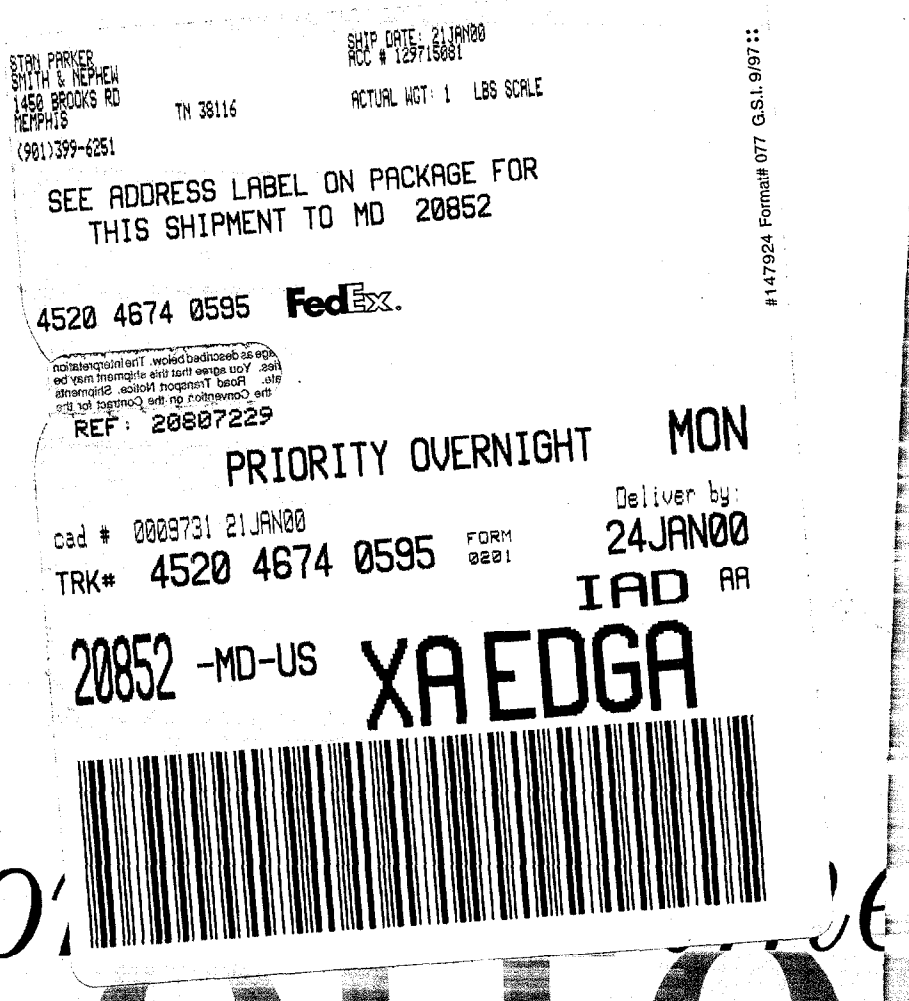

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